Postpartum hemorrhage detection and treatment care pathways and identifying interventions: A decision tree model

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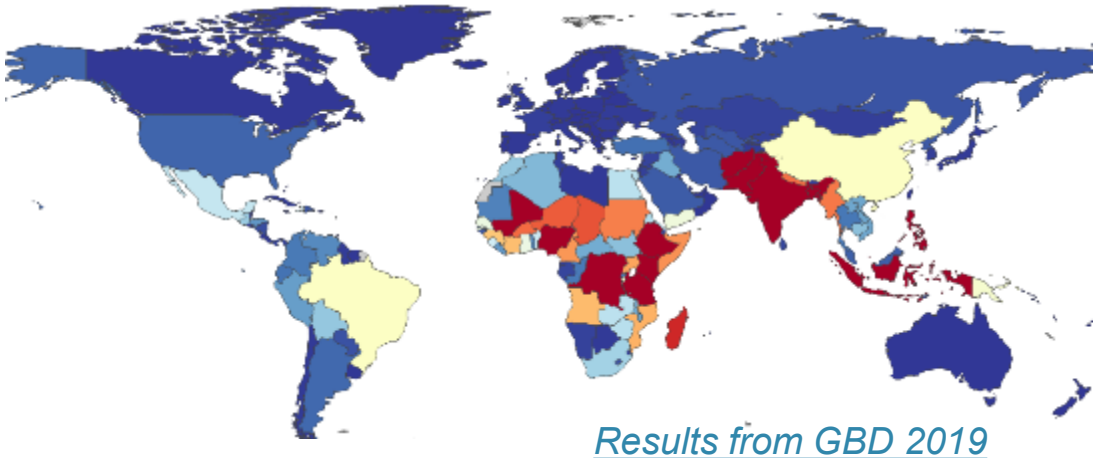
Background

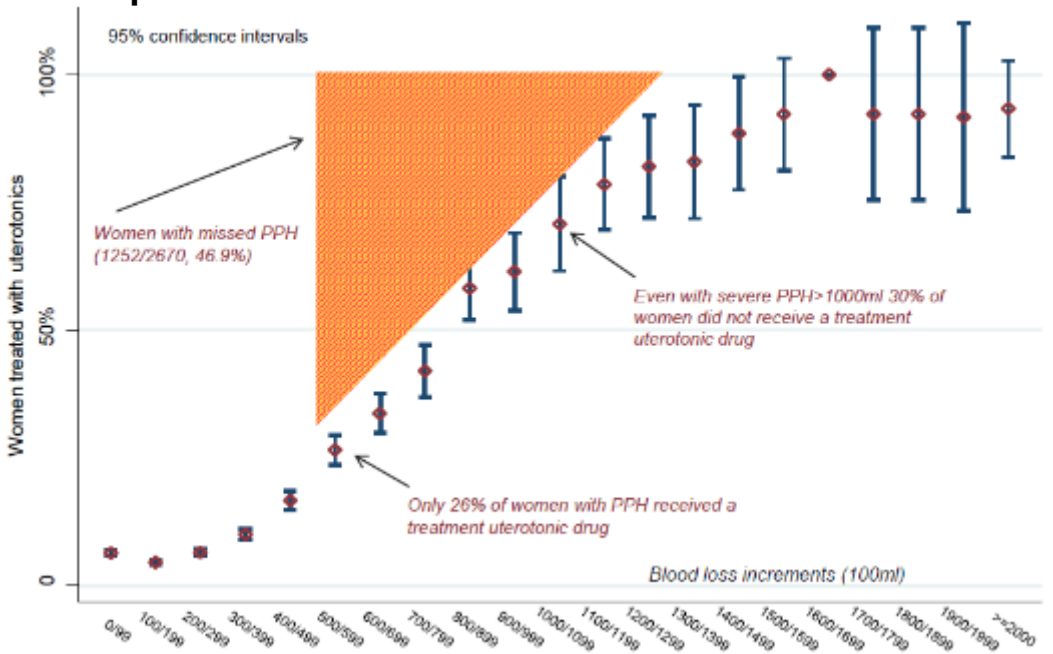
- **Postpartum hemorrhage (PPH)** is one of the leading causes of maternal mortality and morbidity
- The majority of PPH deaths occur in South Asia and sub-Saharan Africa (35,000-65,000 deaths)
- Almost half of women with clinical postpartum hemorrhage are not diagnosed or do not receive the standard of care uterotonics

Postpartum hemorrhage deaths per 100,000 in 2019



Results from GBD 2019

Postpartum blood loss and treatment with uterotonics



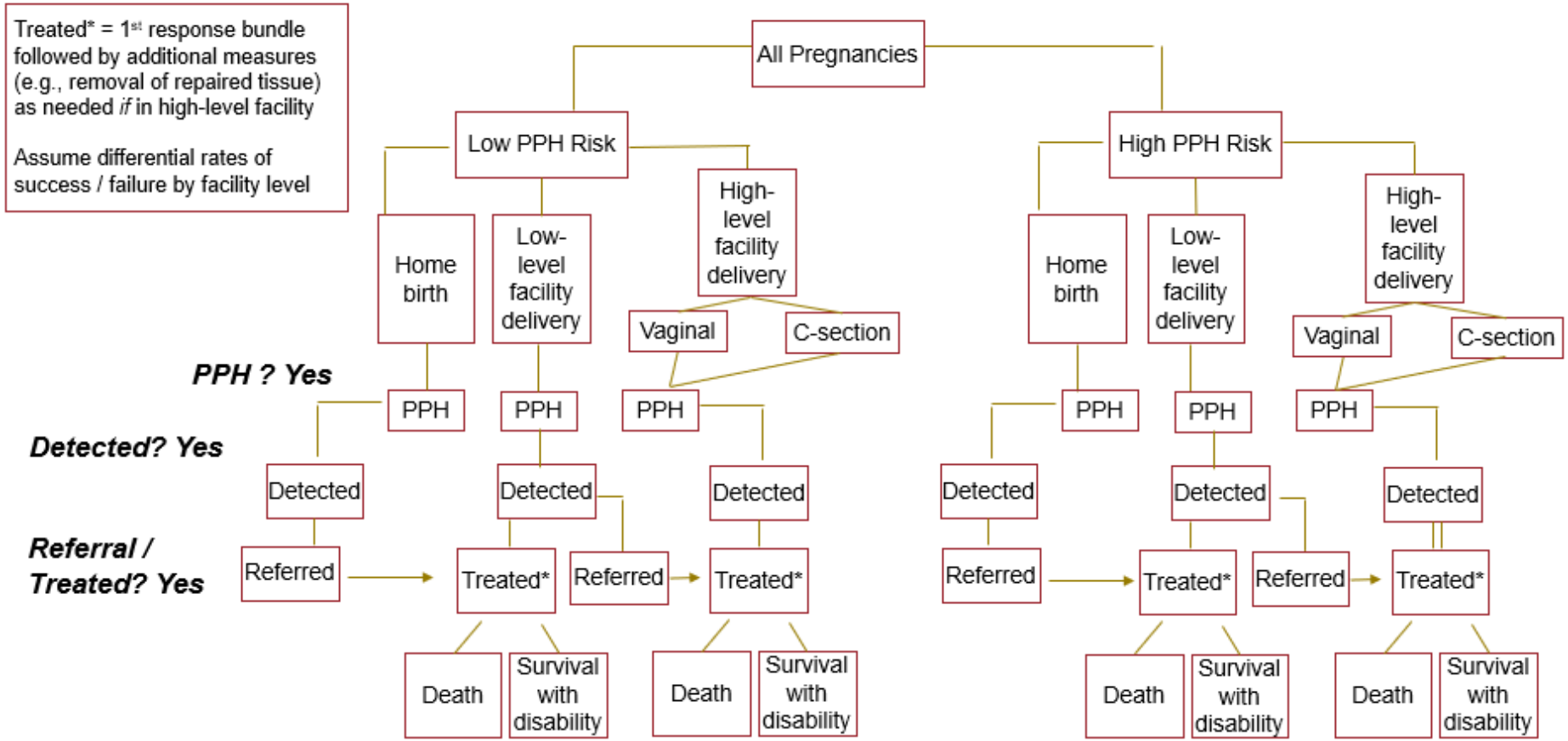
Evidence from the multicenter WHO CHAMPION study

Motivation and Goals

- We built a decision tree model to better understand when and where in a diagnostic and treatment cascade women are suffering and dying from PPH in South Asia and sub-Saharan Africa
  - How is PPH burden distributed by birth location?
  - How is PPH burden distributed among detected/undetected or treated/untreated quality-of-care indicators?
- The model is also built to evaluate intervention impact potential
  - What fraction of PPH burden is prevented? Treated?
  - What is the residual burden after the avertable fraction?
- These results may provide insights into the types of policies or interventions that would reduce this burden of disease

Methods: Overview

- This model is a deterministic decision tree where pregnant women in South Asia and sub-Saharan Africa are segmented into PPH outcomes depending on underlying risk, location of delivery, and diagnostic and treatment coverage
- Outputs include deaths, moderate and severe episodes, years lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life-years (DALYs) lost at many steps of the PPH incidence and treatment pathway



Methods: Input data

Input data from several sources

- Burden (incidence, deaths, disability) and demographics (pregnancies, live births): Global Burden of Disease Study 2019 (GBD)
  - The model is calibrated to match estimates of PPH morbidity and mortality from the GBD (*Supplemental slides*)
- Risk factors and relative risks: Pooled analyses, systematic reviews (*Supplemental slides*)
  - Anemia (35-50% of pregnant women; RR of about 2.7)
  - Home birth (about 30% of births; incidence RR 1.82, mortality RR 4.5)
  - Caesarean Section delivery (5-20% of births; RR 1.85)
- Interventions: **E-MOTIVE (early detection and treatment)***, iron for anemia, other novel interventions
- Uncertainty in input data from published reviews or statistical analyses
- Randomness constructed from draws from distributions of input parameters (*Supplemental slides*)

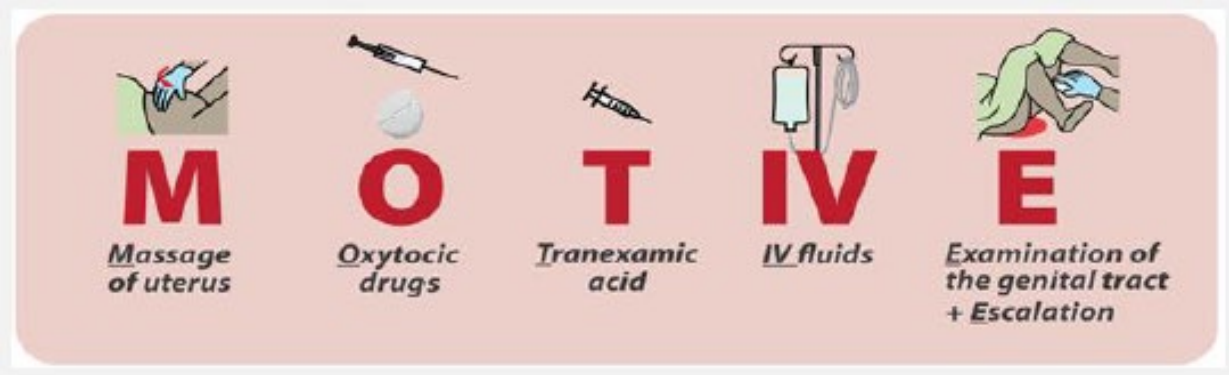
*Gallos et al. NEJM, May 2023

Methods: Forecasts

- We used existing forecasts of live births and the socio-demographic index (SDI) from the Institute for Health Metrics and Evaluation through the year 2040
- The SDI forecasts were used to make predictions of anemia prevalence, in-facility delivery, and Caesarean-section delivery at the country-level and then aggregated to the regional level (South Asia & sub-Saharan Africa)
- Baseline incidence and mortality rates are calibrated to GBD 2019 estimates and we assume changes in PPH outcomes are driven by other parameters in the model including anemia, in-facility delivery, Caesarean-section, live births, and intervention coverage

Interventions: Early detection and case management (E-MOTIVE)

- Early detection and management is crucial for preventing severe episodes and deaths yet almost half of all clinical PPH episodes were not treated with the first-line uterotonic (oxytocin)



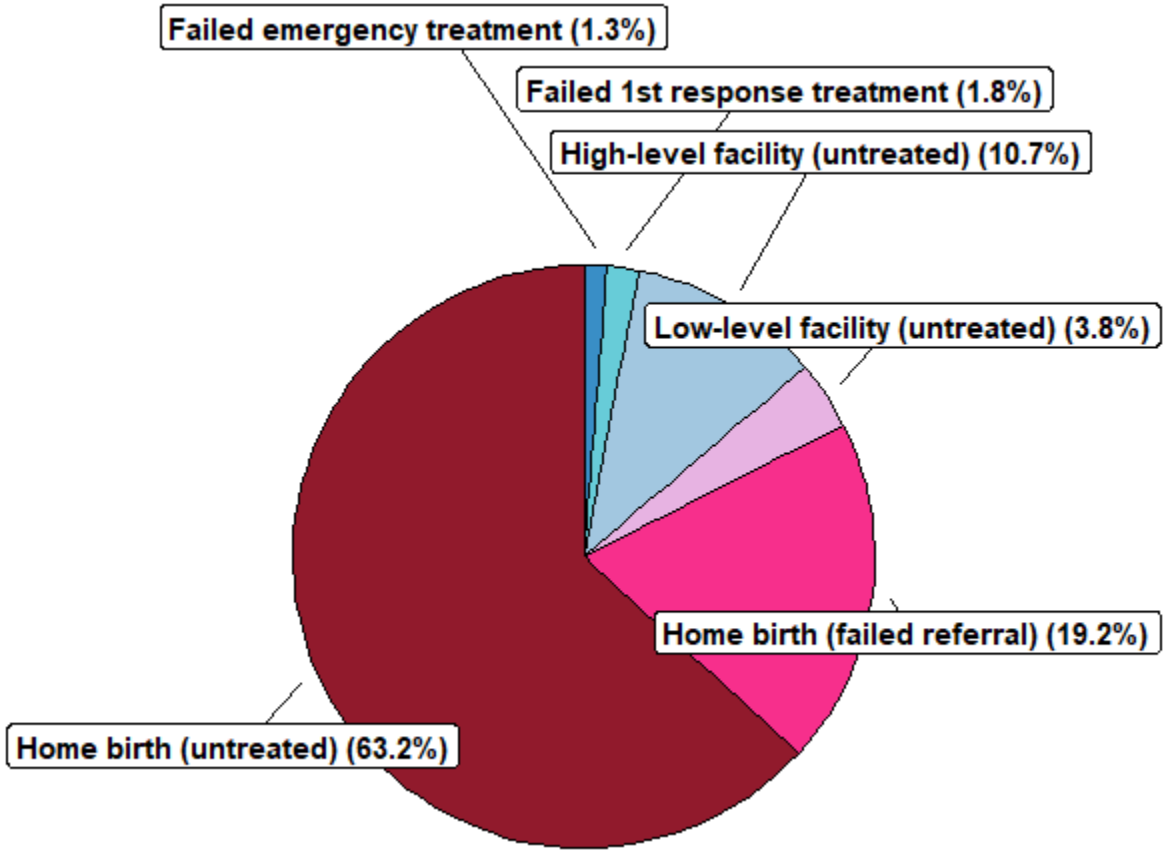
- Scale-up of the E-MOTIVE bundle (**E**arly detection, **M**assage of the uterus, **O**xytocin, **T**ranexamic acid, **IV** fluids, and **E**xamination/**E**scalation). This bundle was very effective in preventing severe PPH in low-income settings (**Relative risk 0.4, 0.32-0.50**)*
  - Diagnostic sensitivity of PPH higher in intervention group (93.1%) compared to control group (51.1%) based on objective measurement of blood loss
  - Compliance with MOTIVE bundle higher in intervention group (91.2%) compared to control group (19.4%)
- Our model considers a scale-up in detection and treatment of PPH following these study results

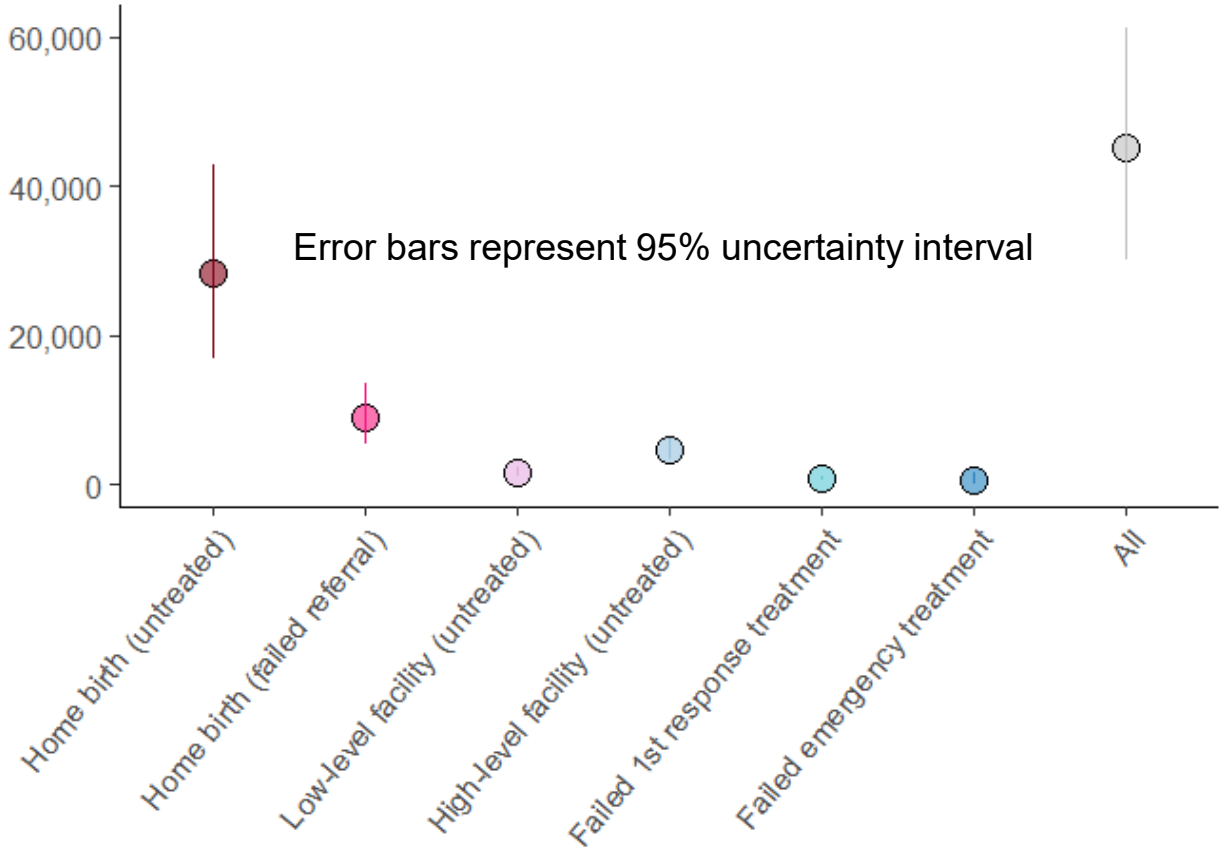
Gallos et al. NEJM, May 2023

Results: Baseline in 2019

- Postpartum hemorrhage is not diagnosed in about 57% of cases and 77.7% of deaths. These women do not receive standard of care including uterotonics (oxytocin), tranexamic acid, or uterine massage.
- Deaths are concentrated in home births: about a third of episodes occurred in home births but four-fifths of deaths occurred in home births

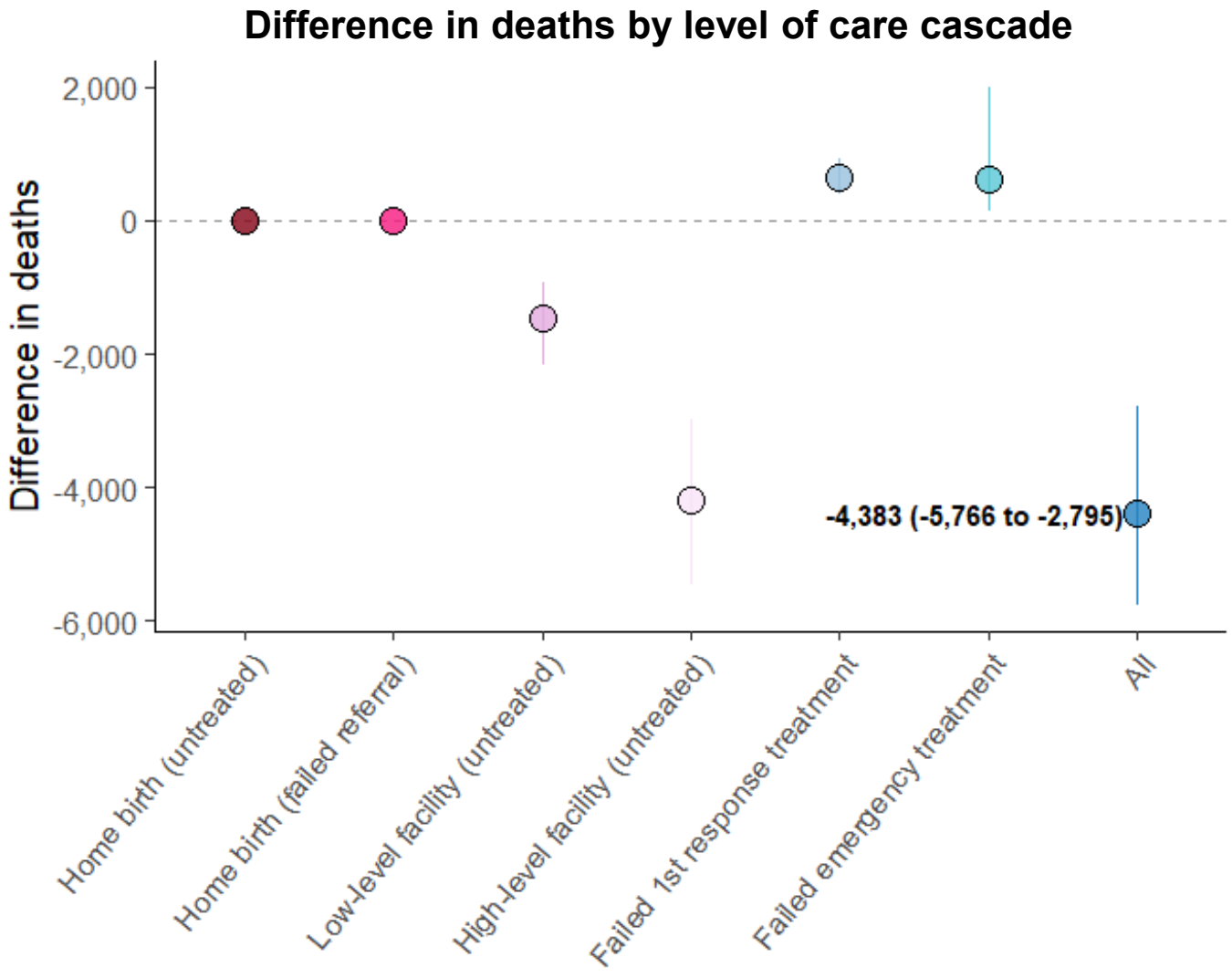
Figures show the percent and number of postpartum hemorrhage deaths at different levels of care cascade



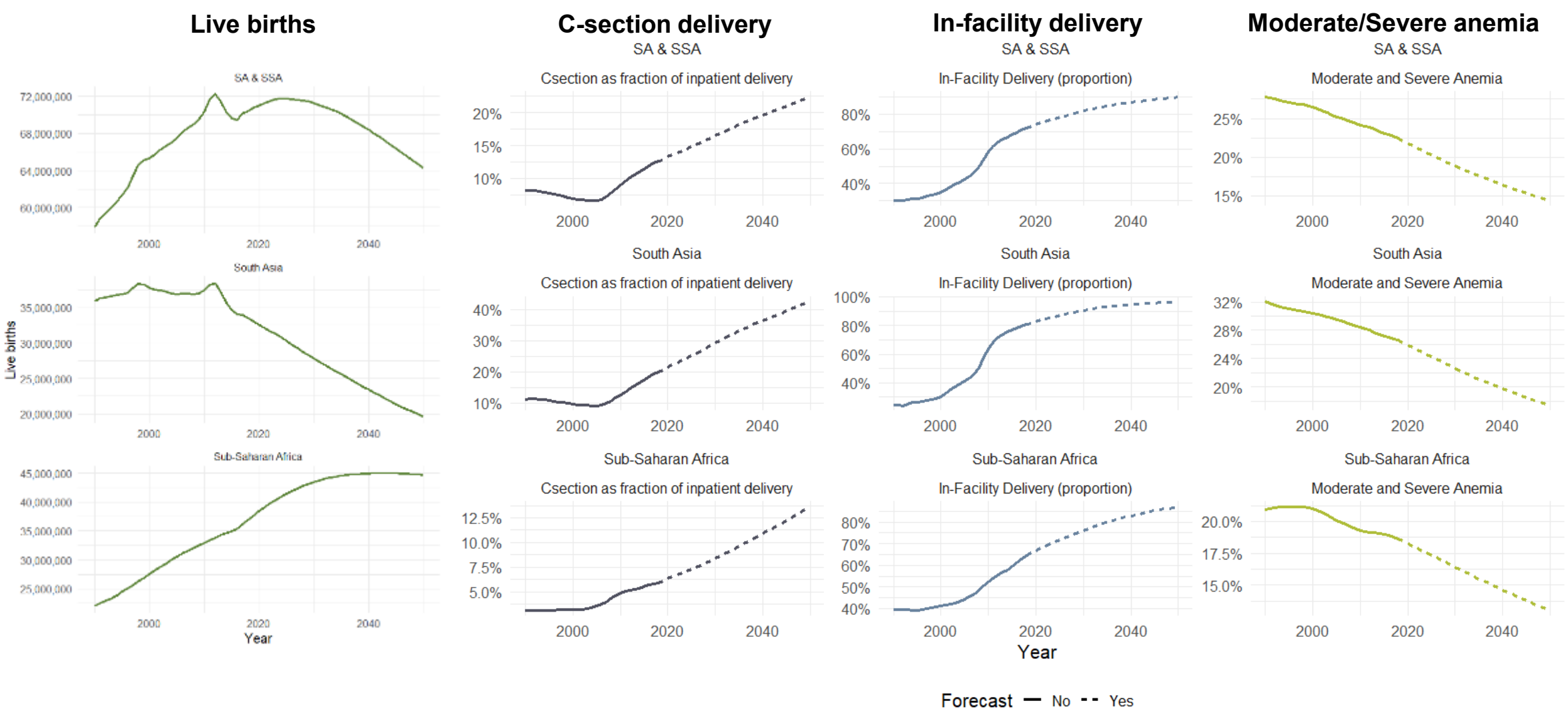


Results: E-MOTIVE bundle counterfactual in 2019

- The E-MOTIVE bundle
  - Increases PPH detection in-facility from about 50 to 90%
  - Increases MOTIVE treatment in-facility from about 20-90%
- Results in about 1,901,000 more episodes diagnosed and treated (95% CI 1,378,000-2,543,000)
- Results in 4,380 fewer deaths in 2019 (95% CI 2,800-5,800)
- Shift in residual deaths due to higher detection but imperfect treatment results in slight increase in deaths occurring after failed standard of care treatment and after failed emergency measures
- Residual deaths are overwhelmingly home births (91.4%)

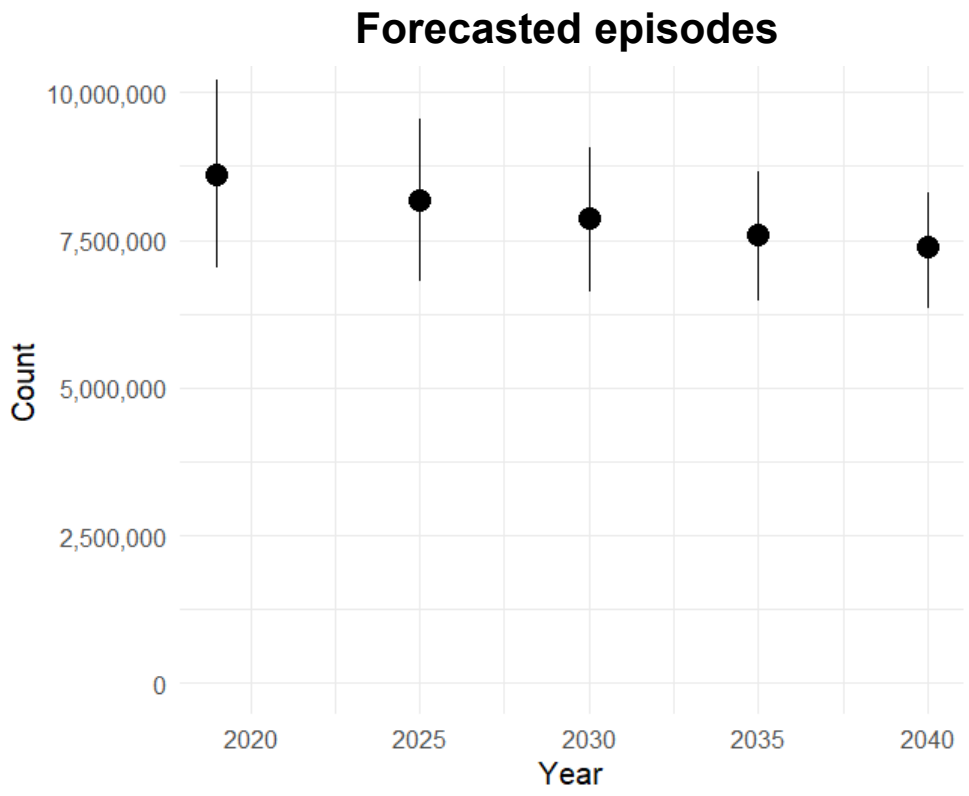


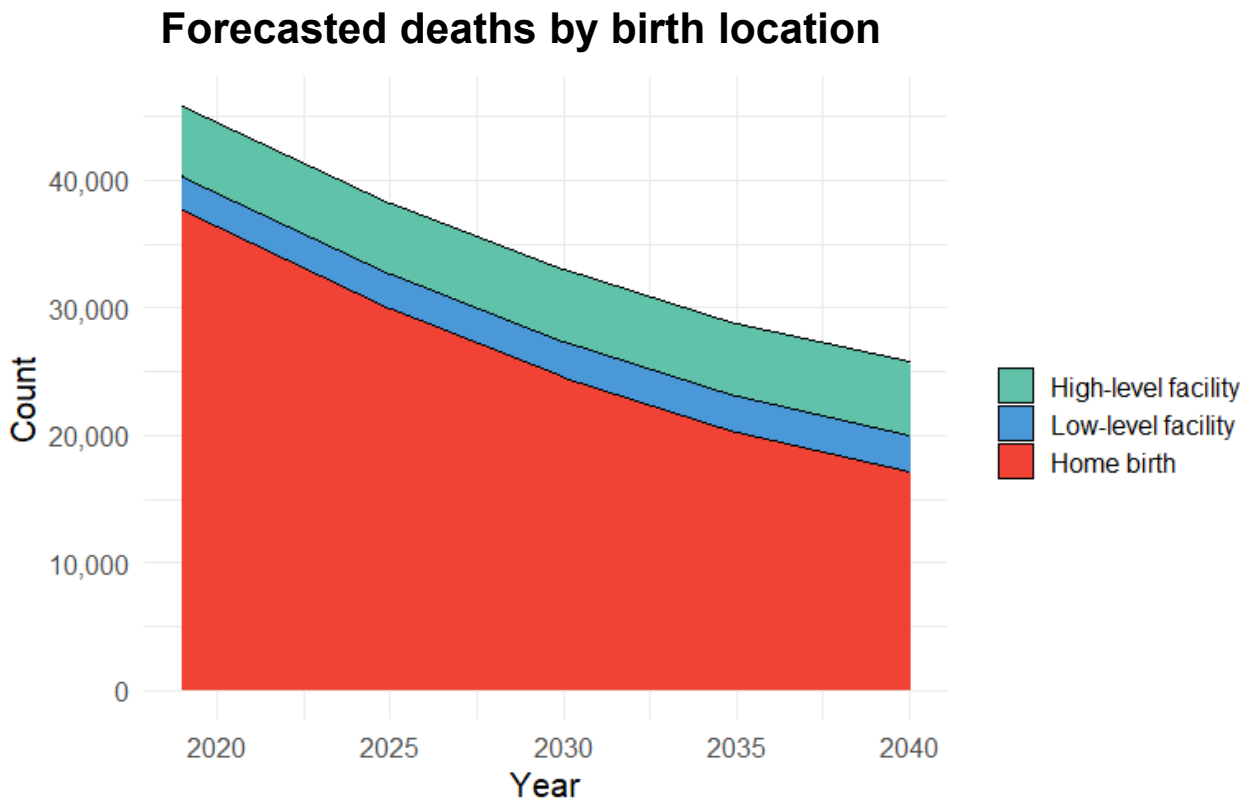
Results: Forecasts of drivers of postpartum hemorrhage



Results: Forecasting postpartum hemorrhage to 2040

- Projected trends in live births, anemia prevalence, C-section delivery, and in-facility delivery suggest a decline in deaths from 44,500 in 2019 to 26,300 in 2040

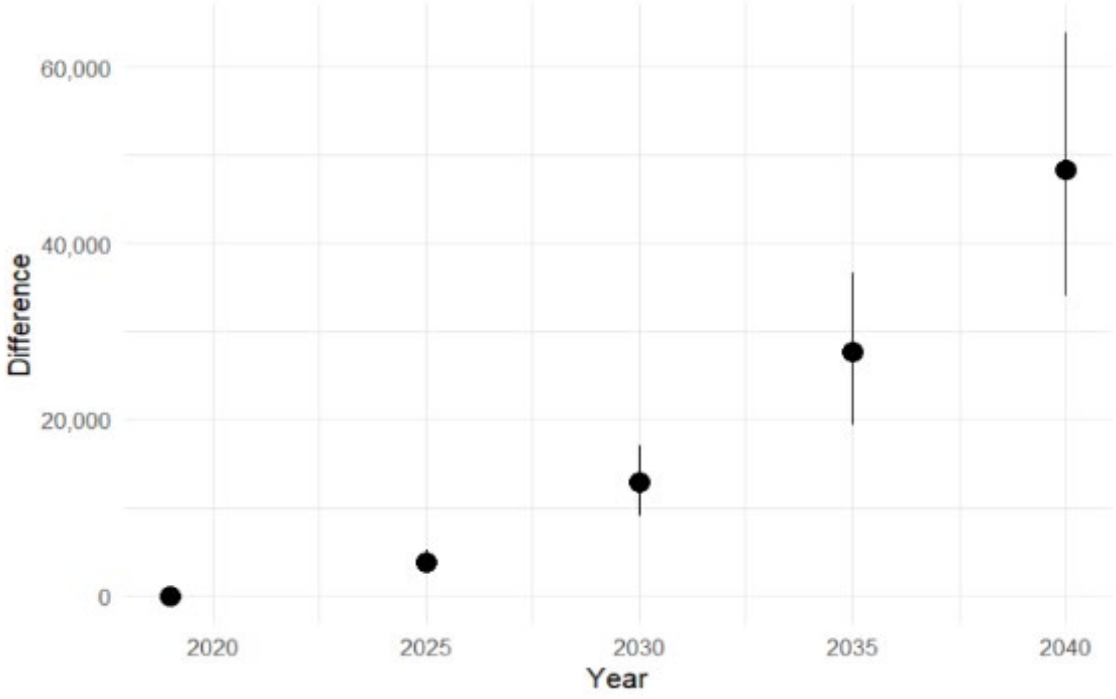




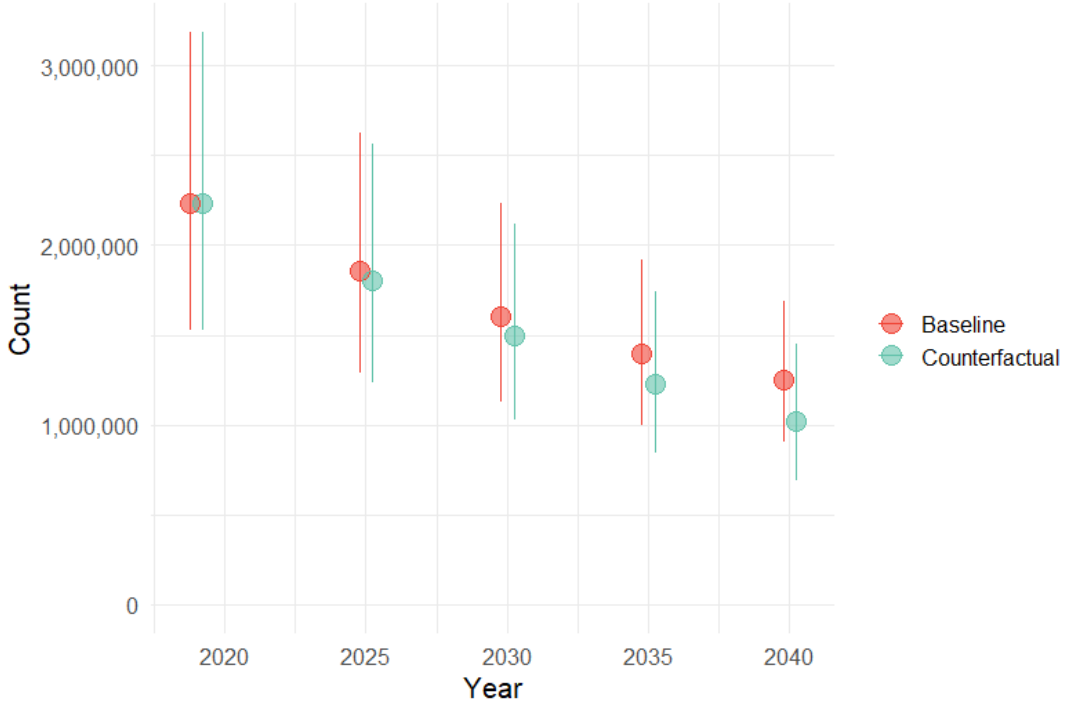
Results: Scale-up E-MOTIVE bundle to 2040

- Scale-up of E-MOTIVE bundle to 90% by 2040 accelerates these trends, averting a cumulative 49,000 deaths (95% CI 32,700-65,000) and 2,253,000 DALYs (95% CI 1,389,000-3,099,000) through 2040

Cumulative deaths averted in counterfactual scenario where E-MOTIVE is scaled-up

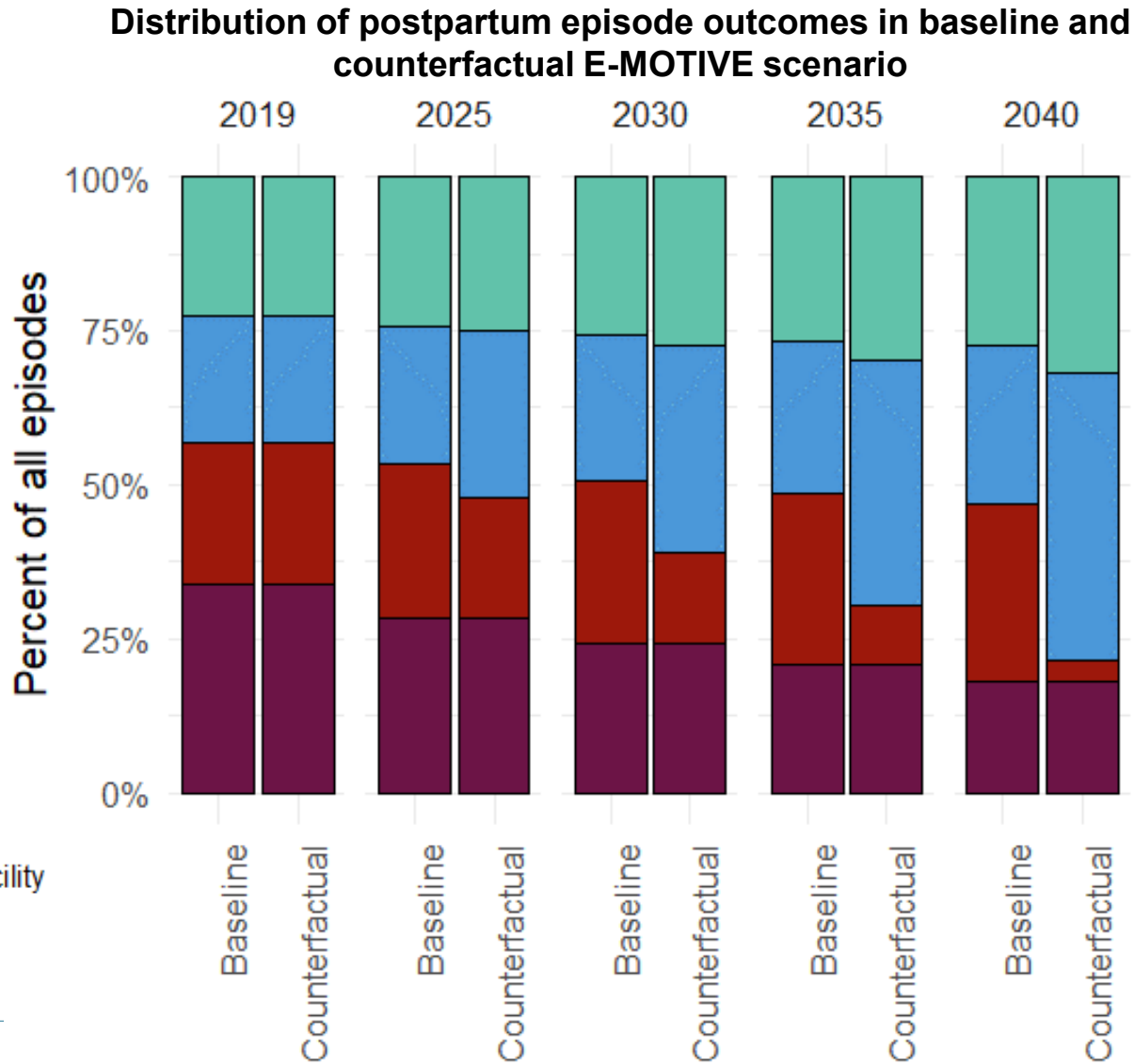


Disability-adjusted life-years (DALYs) in the baseline and E-MOTIVE scale-up scenarios



Results: Residual burden of scale-up E-MOTIVE bundle to 2040

- Increasing coverage of E-MOTIVE also changes the residual addressable burden.
- The fraction of deaths that are detected but unresolved by treatment increases from 15.3% in 2019 to 47.2% in the E-MOTIVE scale-up.
- This is because imperfect effectiveness of treatment results in more detected but unsuccessfully treated episodes.



Interpretation:

- Most postpartum hemorrhage episodes and deaths are never diagnosed and do not receive standard of care including uterotonics, tranexamic acid, uterine massage, or IV fluids (MOTIVE bundle)
- Most postpartum hemorrhage deaths occur in births outside of facilities and this fraction is likely to increase as in-facility detection and treatment improves
- The E-MOTIVE intervention to identify, treat with standard of care, and escalate postpartum hemorrhage episodes could avert 10% of deaths in South Asia and sub-Saharan Africa in 2019 and 50,000 cumulative deaths through 2040
- As more episodes are identified, novel strategies or interventions to treat postpartum hemorrhage are probably required for the residual burden that is not averted with E-MOTIVE
- This segmentation model can be used to understand where and when women suffer from postpartum hemorrhage disability and mortality and to assess potential impact of other interventions

Next steps:

- Refining impact model to test additional counterfactual scenarios
  - Modify risk factors for postpartum hemorrhage including intravenous iron for anemia and AI-enabled ultrasound to support risk-differentiated referral
- Consider strategies to address large residual burden in home births
- More robust estimation of non-fatal disease burden

Thank you and acknowledgements

Thank you to Laura Lamberti and to the MNCH D&T team for support and expertise!

Questions?

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SUPPLEMENTAL SLIDES

Input values for PPH death envelope

- Counts from the Global Burden of Disease study 2019
- Deaths in Nigeria very different between GBD and MMEIG, so:
  - Substitute PPH deaths in Nigeria from GBD with deaths based on MMR from 2018 DHS using the same post-partum cause fraction (~28%; from GBD)
    - [512 * live births / 100,000 * 0.282]
  - Resulting maternal deaths in Nigeria between GBD & MMEIG estimates
- Increases PPH deaths in SA & SSA from about 38,400 to 44,500

Analysis of death estimates from different sources

	Live births (comparison analysis)	MMR	Maternal deaths	PPH deaths	CF PPH
GBD					
South Asia	33,438,486	198	66,342	21,506	32.4%
Sub-Saharan Africa	36,715,355	257	94,439	16,921	17.9%
Nigeria	7,587,167	233	17,650	4,971	28.2%
Total SA & SSA				38,427	
MMEIG					
South Asia	33,567,000	133	44,680	14,364	32.1%
Sub-Saharan Africa	38,255,000	537	205,390	51,626	25.1%
Nigeria	7,698,000	1122	86,380	21,681	25.1%
Total SA & SSA				65,990	
Birmingham					
Sub-Saharan Africa				51,626	25.1%
South Asia				14,364	32.1%
DHS					
Nigeria	7,642,584	512	39,130	11,021	28.2%
Replacing GBD Nigeria with DHS Nigeria					
Sub-Saharan Africa				22,970.70	
Total SA & SSA				44,476.70	

Color Legend
Values from Postpartum Hemorrhage Summit slides
Calculated values from the 2018 Nigeria DHS
Values that go into PPH segmentation model

Number used for this analysis

Supplementary slides: Risk factors and relative risks

Relative risk of PPH incidence given C-section delivery (1.85, 95% CI 1.7, 2.0) [Postpartum Hemorrhage Summit, 2023]

- Prevalence of C-section delivery from GBD 2021

Relative risk of PPH incidence in home birth compared to facility delivery (1.82, 95% CI 1.07-2.61) [Calvert et al. 2012]

Relative risk of PPH death in non-facility to facility delivery (4.5, 95% CI 4.0-5.0) [Calvert et al. 2012]

- In-facility delivery percent from GBD 2019
- Split between high-level and low-level facilities from analysis of CLIP study

Relative risk of PPH given moderate/severe anemia compared to not anemic (2.70, 95% CI 2.0-3.65) [Next slide]

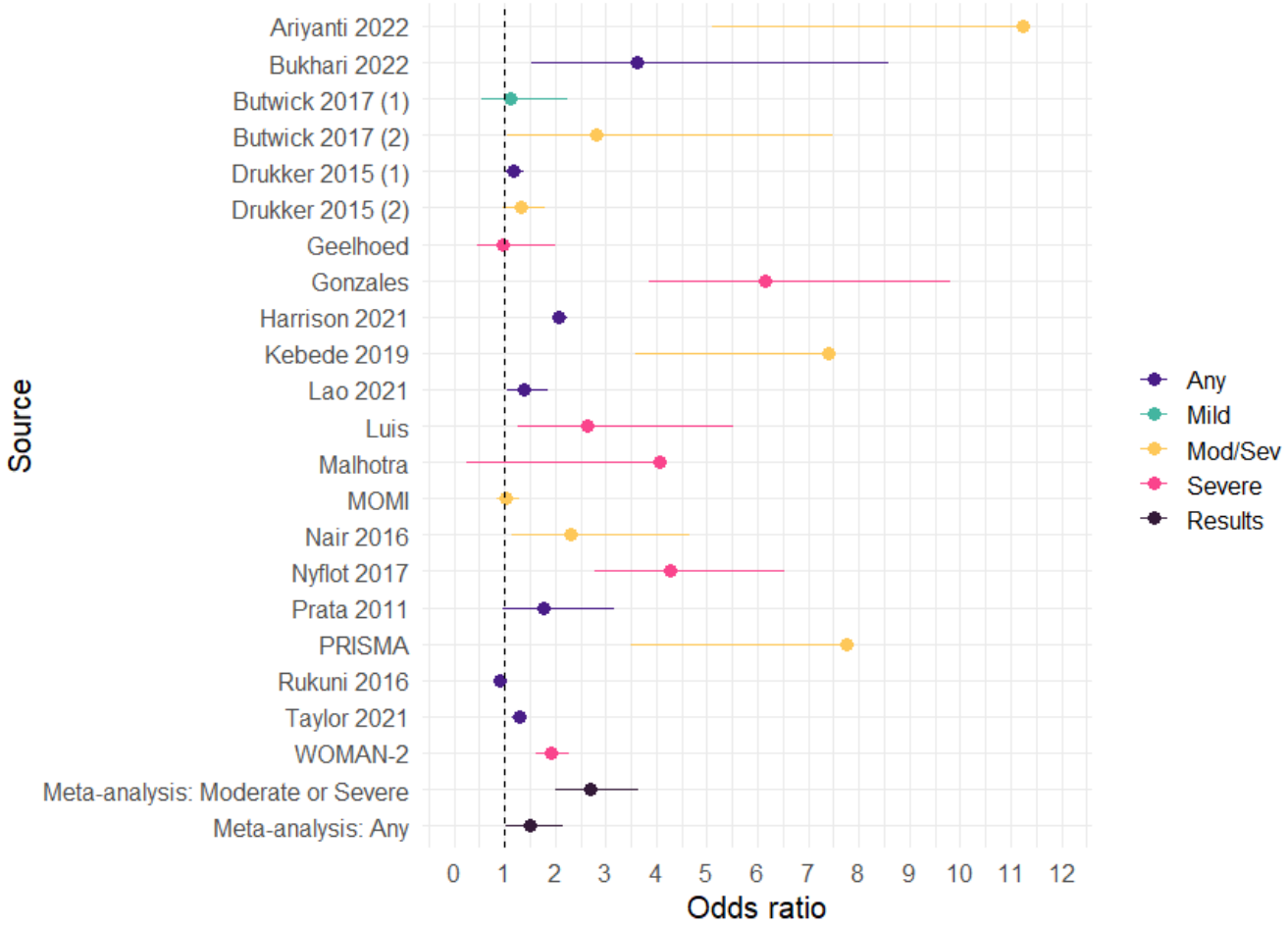
- Anemia prevalence among women 15-49 from GBD 2019

ODDS OF POST PARTUM HEMORRHAGE GIVEN ANEMIA

Uses results from two systematic reviews, supplemented with primary data from MOMI, PRISMA, and WOMAN-2 trials

Moderate/Severe: 2.70 (2.0-3.65)

Any: 1.49 (1.03-2.16)



Supplementary slides: E-MOTIVE study

The NEW ENGLAND JOURNAL of MEDICINE

Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

Ioannis Gallos, D.M.S., M.D., Adam Devall, B.Med.Sci., Ph.D., James Martin, Ph.D., Lee Middleton, M.Sc., Leanne Beeson, B.Sc., Hadiza Galadanci, F.R.C.O.G., Fadhlun Alwy Al-beity, M.D., Ph.D., Zahida Qureshi, M.B., B.S., M.Med., G. Justus Hofmeyr, M.B., B.Ch., D.Sc., Neil Moran, B.M., B.Ch., Sue Fawcus, M.B., B.S., Lumaan Sheikh, F.C.P.S., M.R.C.O.G., et al.

The primary results of a randomized study evaluating the effectiveness of the EMOTIVE bundle was published in May 2023 in NEJM

Study was multi-country, cluster-randomized trial to assess risk of severe PPH, laparotomy, or maternal death due to bleeding in clusters that received the intervention compared to those that didn't

Kenya, Nigeria, South Africa, Tanzania (80 hospitals)

Table 2. Primary Outcomes, Key Secondary Implementation Outcomes, and Secondary Outcomes.*

Outcome	Intervention (N = 49,101)	Usual Care (N = 50,558)	Risk or Rate Ratio (95% CI)†	Difference (95% CI)††
Primary outcome				
Composite of severe postpartum hemorrhage, laparotomy for bleeding, or maternal death from bleeding — no./total no. (%)‡	794/48,678 (1.6)	2139/50,044 (4.3)	0.40 (0.32 to 0.50)§	−2.5 (−3.0 to −2.0)§
Key secondary implementation outcomes				
Detection of postpartum hemorrhage — no./total no. (%)¶	3870/4158 (93.1)	4244/8299 (51.1)	1.58 (1.41 to 1.76)	33.3 (26.9 to 39.8)
Adherence to treatment bundle — no./total no. (%)‖	3791/4158 (91.2)	1623/8351 (19.4)	4.94 (3.88 to 6.28)	70.2 (64.6 to 75.7)
Secondary outcomes				
Postpartum hemorrhage — no./total no. (%)**	4158/48,678 (8.5)	8351/50,043 (16.7)	0.51 (0.44 to 0.60)	−8.2 (−9.7 to −6.6)
Severe postpartum hemorrhage — no./total no. (%)**	786/48,678 (1.6)	2129/50,043 (4.3)	0.39 (0.31 to 0.49)	−2.6 (−3.1 to −2.0)
Laparotomy for bleeding — no. (%)	12 (<0.1)	7 (<0.1)	1.72 (0.57 to 5.16)	0.01 (−0.02 to 0.04)
Maternal death — no. (%)				
From bleeding	12 (<0.1)	18 (<0.1)	0.80 (0.38 to 1.68)	−0.01 (−0.03 to 0.02)
From any cause	17 (<0.1)	28 (0.1)	0.73 (0.40 to 1.31)	−0.02 (−0.04 to 0.01)
Blood transfusion — no. (%)				
For any cause	1074 (2.2)	1296 (2.6)	0.87 (0.69 to 1.10)	−0.4 (−0.9 to 0.2)
For bleeding††	580 (1.2)	944 (1.9)	0.71 (0.55 to 0.90)	−0.6 (−1.0 to −0.2)
Blood loss at ≤2 hr post partum — ml‡‡				
Median (IQR)	160 (100 to 280)	220 (120 to 380)	—	—
Mean	225±229	318±321	—	−84 (−103 to −64)

* Plus–minus values are means ±SD. Laparotomy related to bleeding and maternal death from bleeding were determined by the end-point review committee, whose members were unaware of the trial-group assignments. The widths of the confidence intervals for secondary outcomes have not been adjusted for multiplicity and cannot be used to infer treatment effects.

† Rate ratios are reported for the outcomes of detection of postpartum hemorrhage and use of treatment bundle; risk ratios are reported for other outcomes. Differences between percents are presented in percentage points, and differences between mean values are presented in the unit of the values. Analyses were adjusted for the cluster-level covariates that were used in the randomization (number of vaginal births, prevalence of postpartum hemorrhage, country, and prevalence of primary-outcome events) and for imbalances during the baseline period. Baseline data before implementation of the intervention (involving 110,473 patients in 78 clusters) were disaggregated for the interventional and usual-care sites for each outcome as follows: for the composite primary outcome, 1931 of 50,721 patients (3.8%) in the intervention group and 2546 of 57,012 (4.5%) in the usual-care group; for the detection of postpartum hemorrhage, 5097 of 8179 (62.3%) and 4971 of 9717 (51.2%), respectively; for adherence to the treatment bundle, 1682 of 8194 (20.5%) and 1038 of 9779 (10.6%), respectively; for postpartum hemorrhage, 8194 of 50,720 (16.2%) and 9779 of 57,010 (17.2%), respectively; for severe postpartum hemorrhage, 1920 of 50,720 (3.8%) and 2535 of 57,010 (4.4%), respectively; for laparotomy for bleeding, 10 of 52,003 (<0.1%) and 12 of 58,470 (<0.1%), respectively; for maternal death from bleeding, 16 of 52,003 (<0.1%) and 24 of 58,470 (<0.1%), respectively; for maternal death from any cause, 29 of 52,003 (0.1%) and 34 of 58,470 (0.1%), respectively; for blood transfusion for any cause, 1507 of 52,003 (2.9%) and 1700 of 58,470 (2.9%), respectively; for blood transfusion for bleeding, 991 of 52,003 (1.9%) and 1176 of 58,470 (2.0%), respectively; for median blood loss up to 2 hours post partum, 220 ml (IQR, 120 to 380) and 220 ml (IQR, 120 to 380), respectively; and for median blood loss up to 24 hours post partum, 220 ml (IQR, 120 to 380) and 220 ml (IQR, 120 to 380).

‡ The intracluster correlation coefficient for the primary outcome on the latent scale was 0.011 (95% CI, 0.008 to 0.014). The cluster autocorrelation for the primary outcome was 0.61. The intracluster correlation coefficient and cluster autocorrelation were estimated by fitting a mixed-effects linear model to the data with random effect for cluster and for a cluster–period interaction. In the analysis of severe postpartum hemorrhage, only women with source-verified data on blood loss were included.

§ P<0.001.

¶ The detection of postpartum hemorrhage was defined as the recording of a diagnosis of postpartum hemorrhage by the birth attendant. The denominator is the number of patients with objectively measured postpartum hemorrhage (defined as blood loss of ≥500 ml).

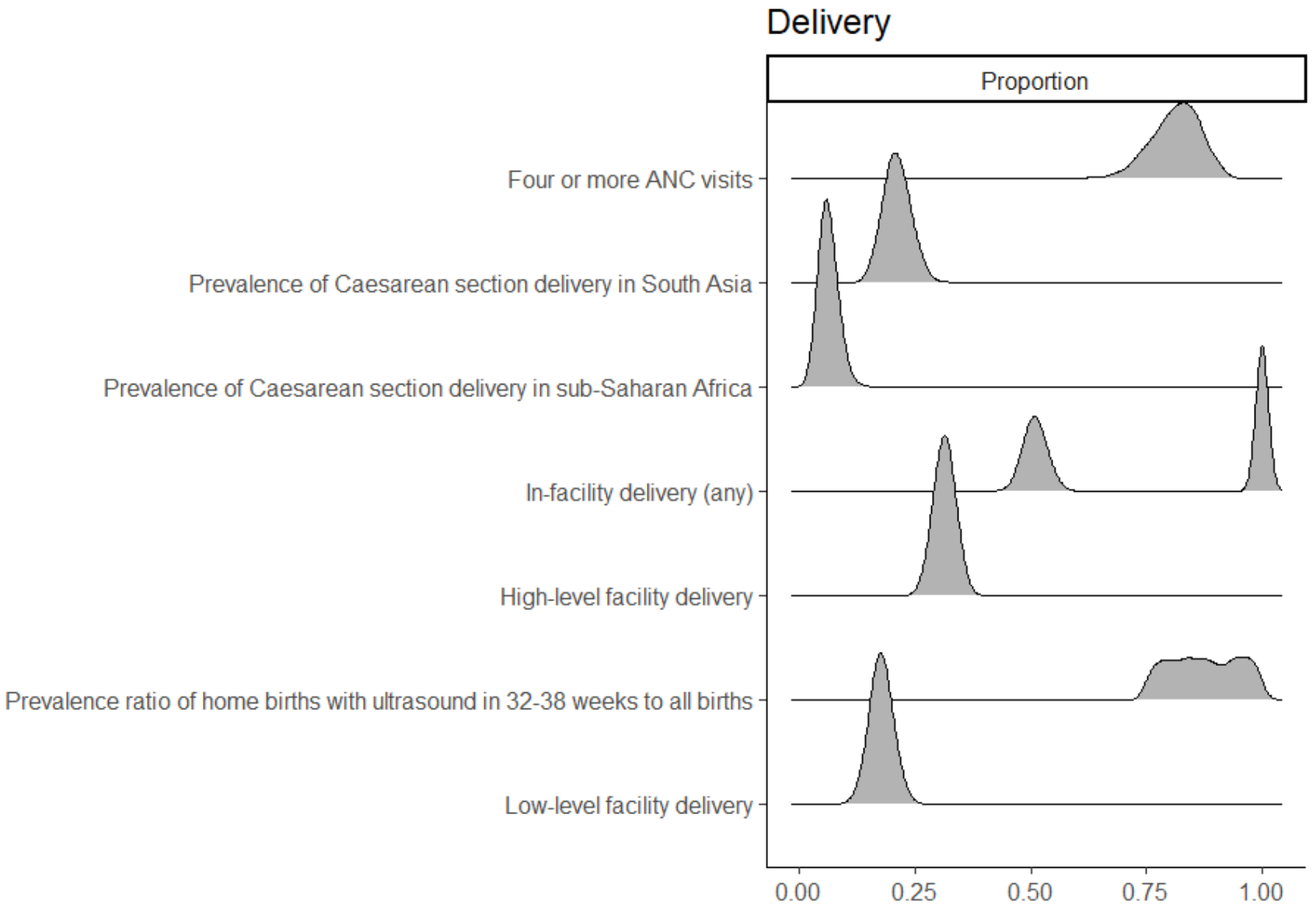
‖ Adherence to the treatment bundle was defined as adherence to three core elements of the bundle: the administration of oxytocic drugs, tranexamic acid, and intravenous fluids. The denominator is the number of patients with objectively measured postpartum hemorrhage.

** Only patients with source-verified data on blood loss were included in this analysis.

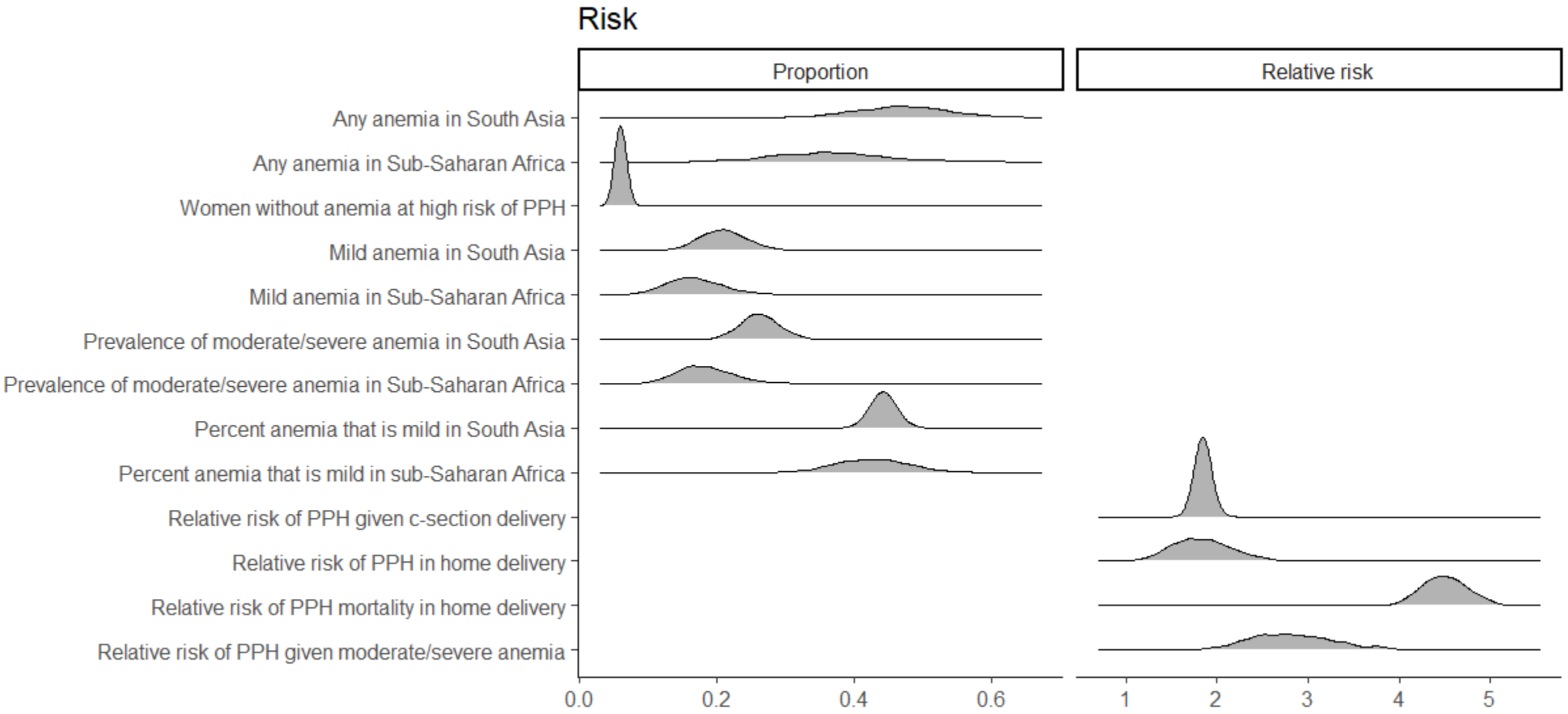
†† Blood transfusion for bleeding was defined as blood transfusion in patients with postpartum hemorrhage.

‡‡ For the analysis of blood loss as a continuous variable, mean differences are reported. Outcomes were analyzed by permutation tests, and confidence intervals were constructed with the use of permutation tests, by finding the upper and lower boundaries of the intervention effect that would lead to a two-sided P value at less than the 5% level.

Supplementary slides: Uncertainty in input parameters



Supplementary slides: Uncertainty in input parameters



Supplementary slides: Uncertainty in input parameters